REMARKS/ARGUMENTS

Favorable reconsideration of this application, in view of the above amendments and in light of the following discussion, is respectfully requested.

Claims 1-22 and Claims 24-27 are pending in the application. Claims 1, 2, 9-14, 20, and 24 are currently amended. Claim 23 is canceled without prejudice or disclaimer. Support for the amendment of Claim 1 can be found in previously presented Claim 23. Support for the amendment of Claims 2 and 24 are self-evident. Support for the amendment of Claim 14 can be found in previously presented Claim 3. Support for the amendment of Claims 9-13 and 20 can be found in the specification as originally filed at page 3, lines 8-10, for example. No new matter is introduced.

As the present amendment combines subject matter that was previously considered, the present amendment is not believed to create any new issues that require further search or consideration. Moreover, MPEP § 714.13 states that (emphasis added) "[a]n amendment filed at any time after final rejection, but before an appeal brief is filed, may be entered upon or after filing of an appeal brief provided that the total effect of the amendment is to (A) remove issues for appeal, and/or (B) adopt examiner suggestions." The present amendment is believed to place the application in better form for appeal by materially simplifying the issues. Accordingly, it is respectfully requested that the present amendment be entered.

In the outstanding Office Action Claims 21-23 and 25 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claim 25 was rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claims 1-2, 4, and 27 were rejected under 35 U.S.C. § 102(b) as anticipated by Ferrara (U.S. Patent No. 4,486,194). Claim 1 was also rejected under 35 U.S.C. § 102(b) as anticipated by Bradley (U.S. Patent No. 532,359). Claims 3, 5-8, 14-19, and 21-25 were rejected under 35 U.S.C. § 103(a) as unpatentable over Ferrara. Claim 26 was rejected under 35 U.S.C. § 103(a) as

unpatentable over Bradley. Claims 9-13 and 20 were rejected under 35 U.S.C. § 103(a) as unpatentable over Ferrara in view of Niemiec (U.S. Patent No. 6,284,234).

During the preparation of this response, Applicants discovered an error introduced by the Amendment filed February 5, 2009. In response to the objection raised by the Office Action mailed October 6, 2008, instances of the word Silkis in the specification and claims were amended to recite calcitrol. As shown in the Appendix to this Amendment, Silkis is the trademark of a composition which includes the ingredient calcitrol.[1] As Silkis includes other ingredients, Silkis and calcitrol are not equivalent. Moreover, the Office Action mailed October 6, 2008 suggested the term "calcitrol *lotion*." Accordingly, Claims 9-13, 20 and the Specification are currently amended to recite "calcitrol *ointment*." Therefore, no new matter is introduced into the specification, and Applicants respectfully request the entry of the present amendments.

With regard to the rejection of Claim 21-22 under 35 U.S.C. § 112(1), the application as originally filed states, for example, the groove (2) has a width of 7 mm and a depth of 2 mm which extends along a longitudinal axis of over 126 mm.[2] One of ordinary skill in the art would recognize based on the above example illustrates a groove including a constant depth and a constant width, as recited in Claim 22. Furthermore, a cross sectional area is defined by the product of a depth and width. Therefore, one of ordinary skill in the art would also recognize that the above example illustrates a uniform cross sectional area as recited in Claim 21. Accordingly, the Applicants respectfully submit that the claimed subject matter was possessed at the time of the application filing and that the rejection of Claims 21 and 22 under 35 U.S.C. § 112(1) be withdrawn.

With regard to the rejection of Claim 25 under 35 U.S.C. § 112(1), as stated above, the specification as originally filed discloses an example of a groove that has a constant depth

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[1] See also http://emc.medicines.org.uk/printfriendlydocument.aspx?documentid=8621&companyid=56.
[2] See the published application at paragraph [0030].

and a constant width. Furthermore, the specification as originally filed states that a first compartment has a length of 14 mm, a second compartment has a length of 28 mm, and a third compartment has a length of 42 mm. Volume is defined as the product of the width, depth, and length. Accordingly, one of ordinary skill in the art would appreciate that the specification as originally filed describes a non-limiting example where the first compartment has a smaller volume than a second compartment, and a second compartment has a smaller volume than third compartment. Therefore the Applicants respectfully submit that they had possession of the claimed invention at the time of the application filing and request that the rejection of Claim 25 under 35 U.S.C. § 112(1) be withdrawn.

With regard to the rejection of Claim 25 under 35 U.S.C. § 112(2), the Applicants traverse the statement that "none of these claims requires that the series includes more than a single compartment."[3] Claim 1 recites an applicator's stick with a longitudinal groove divided into a **series of compartments**. Accordingly, Claim 1 recites a plural series of compartments. Based on the foregoing, the Applicants respectfully submit that Claim 25 is definite and that the rejection under 35 U.S.C. § 112(2) be withdrawn.

Furthermore, the Office Action states that Claim 14 illustrates that Claim 1 requires no more than a single compartment.[4] As stated above, Claim 1 requires a plural, series of compartments. However in light of the Office Action, amended Claim 14 clarifies that the groove includes a first, second, third, and fourth compartments. This amendment is consistent with previously presented Claim 3.

Amended independent Claim 1 recites an applicator stick that includes a longitudinal groove divided into a series of compartments. Amended Claim 1 incorporates the feature *graduations provided perpendicular to the groove, that extends from a top surface of the applicator stick in a depth direction of the groove,* from previously presented Claim 23.

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[3] See the Office Action at page 3, lines 12-15.
[4] See the Office Action at page 3, lines 13-14.

Furthermore, amended Claim 1 clarifies that the graduations extend from a top surface of the applicator stick. Amended Claim 1 further recites that the groove defines an uncovered depression in *the top surface* of the applicator. Accordingly, amended Claim 1 requires that the groove extend from the top surface of the applicator stick and that the graduations extend from the top surface of the applicator stick in a depth direction of the groove.

As Claim 1 now recites the features of Claim 23, the Applicants respectfully traverse the rejection of previously presented Claim 23 under 35 U.S.C. § 112(1). MPEP § 2163.06 states: "information contained in any one of the specification, claims, or drawings of the application as filed may be added to any other part of the application without introducing new matter." (Emphasis added.) Indeed, MPEP § 2162(I) states: "an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention."[5] Figure 1 of the disclosure as originally filed fully satisfies the written description requirement, with respect to the features of previously presented Claim 23.

As can be seen from Figure 1 of the original disclosure, the graduation (4) extends from the *top surface* of the applicator stick (1) in a depth direction of the groove (2). This feature can also be appreciated by Figures 2 and 4 of the original disclosure. The Applicants note that the claimed invention is not limited to these examples, but that the above example is solely intended to demonstrate that the Applicants had possession of the claimed invention without precluding any equivalents thereof. Accordingly, the Applicants respectfully request that the rejection of the features of previously presented Claim 23 under 35 U.S.C. § 112(1) be withdrawn.

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[5] Quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997), emphasis added.

The Applicants respectfully traverse the rejection of amended Claim 1 as anticipated by the cited references.

Figure 1 of Ferrara illustrates a therapeutic device (10) that includes an inner supporting member (12) that is provided with walls (22) defining a chamber (24).[6] As can be seen in Figure 1 of Ferrara, the support member (12) includes indicia of measurement represented by lines (28) and numerals (30).[7] Furthermore as illustrated in Figure 4 of Ferrara, raised members (34) may be used instead of lines (28).[8] However, amended Claim 1 requires that both the groove and the graduations extend from the top surface of the applicator stick.

As can be seen in Figure 1 of Ferrara, the lines (28) do not extend from the top surface of the device (10) nor do they travel in a depth-wise direction along the walls (22). Furthermore, Figure 4 of Ferrara illustrates that the raised members (34) also do not extend from the top surface of the device (10) nor do they extend along the walls (22) in a depth-wise direction. Accordingly, Ferrara does not suggest or disclose all of the features of amended independent Claim 1.

Bradley fails to cure the deficiencies of Ferrara. Figure 3 of Bradley illustrates a rod with a straight groove to be filled with a semi-solid medicine.[9] However, the groove of Bradley does not suggest or disclose a series of compartments. Moreover, Bradley does not suggest or disclose graduations provided perpendicular to the groove that extends from the top surface of the rod in a direction of the groove. Accordingly, Bradley does not suggest or disclose all of the features of amended independent Claim 1.

Furthermore, the Office Action fails to provide a clearly articulated apparent reason as to why graduations provided perpendicular to the groove, that extend from a surface of the

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[6] See Ferrara at column 2, lines 45-55.
[7] See Ferrara at column 2, lines 57-60.
[8] See Ferrara at column 3, lines 7-10.
[9] See Bradley at column 1, lines 25-50.

applicator stick in a depth direction of the groove, would be obvious.[10] As such, the Office Action fails to make a *prima facie* case of obviousness. As noted in MPEP § 2142, the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) states that the analysis supporting a rejection under 35 U.S.C. §103 should be made *explicit* (emphasis added). Moreover, the Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."[11] The Applicants respectfully submit that a statement that it would have been obvious in light of the teachings of Ferrara that it would be been obvious for one of ordinary skill in the art to modify Ferrara to include graduations of amended Claim 1,[12] does not meet the burden set forth in MPEP § 2142.

Based on the foregoing, even the combined teachings of Ferrara and Bradley do not suggest or disclose all of the features of amended independent Claim 1. Accordingly, the Applicants respectfully submit that amended independent Claim 1 is in condition for allowance.

It is also respectfully submitted that the cited references fail to suggest or disclose the numerous features set forth in the present dependent claims. Accordingly, the Applicants respectfully submit that dependent Claims 2-22 and 24-27 are in condition for allowance for at least the same reasons as amended independent Claim 1 from which they depend.

For example, dependent Claim 5 recites that the first compartment is able to contain a quantity of composition corresponding to an area of 0.8 to 1.2% of a total surface of a body. The Office Action acknowledges that Ferrara does not teach this limitation, yet dismisses the feature as a mere result effective variable.

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[10] See the Office Action mailed May 5, 2009, at number 21.
[11] See, *In re Kahn*, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval).
[12] See the Office Action mailed May 5, 2009, at number 21.

MPEP § 2144.05(ii)(B) states:

> A particular parameter **must first be recognized as a result-effective variable**, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

Ferrara, however, does not define or dimension a percentage of a surface of a body. Nor is it discernable if the invention of Ferrara effects any percentage of the total surface of the body beyond the portion that the device is directly attached. Furthermore, Ferrara is absolutely silent with respect to any particular result being achieved by an amount of composition to correspond to a variable percentage of a total surface of the body. As Ferrara has not recognized that the change of percentage in Claim 5 achieves any recognized result, the claimed range is not a matter of routine optimization. Accordingly, Ferrara does not disclose or suggest the features of dependent Claim 5, and the Applicants respectfully submit that Claim 5 is in condition for allowance.

For the reasons discussed above, no further issues are believed to be outstanding in the present application, and the present application is believed to be in condition for formal allowance. Therefore, a Notice of Allowance for Claims 1-22 and 24-27 is earnestly solicited.

Should the Examiner deem that any further action is necessary to place this application in even better condition for allowance, Examiner is encouraged to contact the Applicants' undersigned representative at the below-listed telephone number.

Respectfully submitted,

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Appendix

Silkis Product Information

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Summary of Product Characteristics last updated on the eMC: 24/08/2009

Silkis 3 micrograms per g ointment

1. NAME OF THE MEDICINAL PRODUCT

Silkis 3 micrograms per g ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of ointment contains 3 micrograms of calcitriol (INN).

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Ointment

White, translucent ointment

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of mild to moderately severe plaque psoriasis (psoriasis vulgaris) with up to 35% of body surface area involvement.

4.2 Posology and method of administration

Silkis Ointment should be applied to the psoriasis affected areas twice per day, once in the morning and once in the evening before retiring and after washing. It is recommended that not more than 35% of the body surface be exposed to daily treatment. Not more than 30 g of ointment should be used per day. There is limited clinical experience available for the use of this dosage regimen of more than 6 weeks.

There is no experience of the use of Silkis in children (see 4.4. Special Warnings and Precautions for Use). Patients with kidney or liver dysfunction should not use Silkis (see also 4.3. Contra-indications).

4.3 Contraindications

Patients on systemic treatment of calcium homeostasis.

Patients with kidney or liver dysfunction.

Patients with hypercalcaemia and patients known to suffer from abnormal calcium metabolism.

Silkis must not be used in patients known to be hypersensitive to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

The ointment can be applied to the face with caution, as there is an increased risk of irritation in this area. Contact with the eyes should be avoided. The hands should be washed after applying the ointment in order to avoid unintentional application to non lesional areas. Not more than 35% of the body surface should be exposed to daily treatment. Not more than 30g of ointment should be used per day.

Due to potential effects on calcium metabolism, substances which stimulate absorption must not be added to the ointment, and the ointment must not be covered with an occlusive dressing.

In case of severe irritation or contact allergy, the treatment with Silkis should be discontinued and the patient should obtain medical advice. If contact allergy is demonstrated this discontinuation is definitive.

In view of the particular sensitivity of neonatal versus adult rodents to the toxic effects of calcitriol, exposure of children to calcitriol ointment should be avoided (see also 4.2. Posology and Method of

administration)

Although no clinically significant hypercalcaemia was observed in clinical studies with a dosage under 30 g/day of Silkis ointment, some absorption of calcitriol through the skin does occur and excessive use of the ointment can lead to systemic side-effects, such as an increase in urine and serum calcium levels.

There is no information about the use of Silkis in other clinical forms of psoriasis (other than plaque psoriasis) *i.e.* Psoriasis guttata acuta, pustular psoriasis, psoriasis erythrodermica and rapid progressive plaque psoriasis.

4.5 Interaction with other medicinal products and other forms of interaction

Silkis must be used with caution in patients receiving medications known to increase the serum calcium level, such as thiazide diuretics. Caution must also be exercised in patients receiving calcium supplements or high doses of vitamin D. There is no experience of the concurrent use of calcitriol and other medications for the treatment of psoriasis.

Information of interaction of systemic medications after the use of calcitriol ointment is limited. As no relevant elevation of plasma level is seen after the use of calcitriol on the skin, interaction with systemic medication is unlikely.

Silkis Ointment has a slight irritant potential, and therefore, it is possible that concomitant use of peeling agents, astringents or irritants products may produce additive irritant effects.

4.6 Pregnancy and lactation

Use during Pregnancy:

There are no adequate data from the use of Silkis in pregnant women. Studies in animals have shown developmental toxicity at doses which caused maternal toxicity (see section 5.3). The potential risk for humans is unknown.

Silkis should only be used during pregnancy in restricted amounts when clearly necessary. Calcium levels should be monitored.

Use during Lactation:

Calcitriol has been found in milk of lactating dams. Due to the lack of human data, it should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Between 10% and 20% of patients can be expected to experience adverse reactions. Adverse reactions are usually localised to the application site and mild to moderate in nature.

Very common adverse reactions: Adverse reactions occurring in ≥ 1/10 of patients.

Common adverse reactions: Adverse reactions occurring in ≥ 1/100, <1/10 of patients.

Uncommon adverse reactions: Adverse reactions occurring in ≥ 1/1000, <1/100 of patients.

Rare adverse reactions: Adverse reactions occurring in ≥ 1/10000; <1/1000 of patients.

Very rare adverse reactions: Adverse reactions occurring in <1/10000 of patients

Adverse reactions reported by more than two patients in the clinical studies are included.

System Organ Class	Frequency	Preferred term
Skin and Subcutaneous disorders	Common	Pruritus, Skin discomfort, Skin irritation, Erythema
	Uncommon	Dry skin, Psoriasis (aggravated)

In case of severe irritation or contact allergy, the treatment with Silkis should be discontinued and the patient should obtain medical advice. If contact allergy is demonstrated this discontinuation is definitive.

4.9 Overdose

The most common symptoms which may occur after accidental administration are anorexia, nausea, vomiting, constipation, hypotonia and depression. Lethargy and coma are occasionally observed. If hypercalcaemia or hypercalciuria occurs, the use of Silkis should be discontinued until the serum or urinary calcium levels have returned to normal.

If the medication is applied excessively no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: D 05AX03

Calcitriol inhibits the proliferation and stimulates differentiation of keratinocytes. Calcitriol inhibits proliferation of T-cells and normalises the production of various inflammation factors.

Topical administration of Silkis Ointment to patients with plaque psoriasis results in an improvement of the skin lesions. This effect is noted from 4 weeks after the start of treatment.

5.2 Pharmacokinetic properties

The mean absorption of calcitriol is estimated at around 10%. Following absorption, both unchanged calcitriol and metabolites have been demonstrated in plasma. The effect of the metabolites on calcium homeostasis is negligible. In most patients, circulating levels of exogenous calcitriol are below the level of detection (2pg/ml).

In clinical trials, no relevant increase in plasma calcitriol levels after treatment of large body surface areas of up to 6000 cm^2 (35% body surface area) was noted.

5.3 Preclinical safety data

Animal studies show that repeated excessive exposure to calcitriol leads to renal failure and tissue calcification due to hypervitaminosis D associated with hypercalciuria, hypercalcaemia, and hyperphosphataemia.

No indication of teratogenicity was observed in embryofoetal toxicity studies designed to assess the teratogenic potential of calcitriol. Some evidence of developmental toxicity was obtained in a cutaneous rabbit study at doses which caused maternal toxicity. No such effect was found in rats.

Local toxicity studies in animals with Calcitriol showed slight skin and eye irritation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid paraffin, white soft paraffin and alpha- tocopherol.

6.2 Incompatibilities

There are no relevant data on the compatibility of Silkis with other medicinal products. Therefore, Silkis should be used according to the posology and method of administration provided above (Section 4.2), and should not be mixed with other medicinal products.

6.3 Shelf life

3 years

Shelf life after first opening : 8 weeks.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

The product is packaged in collapsible aluminium tubes coated internally with an epoxy - phenolic resin and fitted with a white high density polyethylene or polypropylene screw cap. Tubes contain either 15, 30 or 100g of ointment.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

Galderma (UK) Limited

Meridien House

69-71 Clarendon Road

Watford

Herts

WD17 1DS

UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 10590/0047

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.07.1995 / 09.02.2004

10. DATE OF REVISION OF THE TEXT

03/08/2009